DETAILED ACTION

This office action is in response to a Response to Restriction requirement filed 7/16/08. It is noted that the restriction requirement mailed 6/27/08 to the claims in group I and II as 1-8 and 10-12. However, the members of Group II, drawn to a cell comprising a reporter gene should have been listed as claims 13-22. As applicants have elected Group I and these claims were properly listed, a new restriction requirement will not be mailed.

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on 7/16/08 is acknowledged. The traversal is on the ground(s) that no search burden is afforded by searching groups I and Ii together. This is not found persuasive because as to the relatedness of the instant invention, restriction practice based upon inventive concept serves as guidance for lack of unity practice which follows for cases filed under 35 USC 371. Specifically, PCT rules teach that "Any international application must relate to one invention only or to a group of inventions so linked as to form a single general inventive concept (PCT Article 3(4)(iii) and 17(3)(a), PCT Rule 3.1, and 37 CFR 1.475)." PCT Rule 13.2 requires that unity of invention exists only when the shared same or corresponding technical feature is a contribution over the prior art. In this case, prior art has demonstrated that the use of a cell comprising a reporter gene operably lined to a regulatory sequence responsive to Aphidicin, Trichostatin A, sodium butyrate, SAHA and MS27-275 is not a contribution over the art, see figure 3 of 20040241653).

The requirement is still deemed proper and is therefore made FINAL.

Claims 13-22 are withdrawn from consideration as being drawn to nonelected inventions, Claims 1-8 and 10-12 are examined herein.

Information Disclosure Statement

IDS' filed 6/12/06 and 5/18/07 have been identified. A number of the references in the IDS filed 5/18/07 were duplicates of the references filed 6/12/06. Duplicated references were crossed off of the 1449.

Priority

In an amendment filed 4/18/02, applicants have amended the priority data to read that the instant application claims priority to PCT/EP2004/014159, which claims priority to US application 60/530,540. While the priority claim reads that the instant application claims priority to PCT/EP2004/014159, it is unclear if the instant application is a continuation or 371 of PCT/EP2004/014159. According to the MPEP 1895.01, the specific reference must identify the parent international application by international application number and international filing date and indicate the relationship of the applications (i.e., continuation, continuation-in-part, or division). An example of an appropriate first sentence of the specification is, for example, "This is a 371 of International Application PCT/EP2004/014159, with an international filing date of 12/10/04."

Claim Objections

Claim 1 is objected to because of the following informalities: claim 1 recites "providing cells which include a reporter gene" which for grammatical consistency should recite --providing a cell which includes a reporter gene-- as a reporter gene can not be contained in a number of cells. Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 and 10-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is drawn to a genus of transcriptional regulatory sequences that are responsive to HDAC inhibitors Apicidin, Trichostatin A, sodium butyrate, SAHA and MS27-275. As well, applicants claim a genus of reporter genes encoding an enzyme wherein the activity of enzyme is detected by culturing the cell comprising gene with the enzymatic substrate. The written description requirement under 35 USC 112, first paragraph may be met by sufficient description of a representative number of species by

actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Applicant is referred to the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov).

The specification teaches a method of identifying novel histone deacetylase inhibitors (HDAC) by use of a cell comprising transcriptional regulatory sequences that is responsive to HDAC inhibitors Apicidin, Trichostatin A, sodium butyrate, SAHA and MS27-275. As well, in claim 6, applicants recite that the transcription regulatory sequence includes p21WAFI/CIP1 transcription regulatory sequence that does not include nucleotide sequences responsive to p53. This is thus a genus of regulatory sequences. To this end, applicants teach more specifically, use of p21 WAF1/CIP1 transcription regulatory sequences, which include sequences responsive to HDAC inhibitors Apicidin, Trichostatin A, sodium butyrate, SAHA and MS27-275. Specifically on page 5, the specification teaches, "In a further aspect of the cell comprising a reporter gene operably linked to a p21WAF1/CIP1 transcription regulatory sequence, the p21WAFI/CIP1 transcription regulatory sequence does not include nucleotide sequences responsive to p53 and preferably includes the nucleotide sequence from about nucleotide -183 to nucleotide +25 of the p21WAFI/CIP1 transcription regulatory sequence or includes the nucleotide sequence set forth in SEQ ID NO: 1. In a particular aspect, the cell comprising a reporter gene operably linked to a p21WAF1/CIP1 transcription

regulatory sequence is ICLC PD02008". Hence, applicants only teach SEQ ID NO:1 and more specifically as relates to claim 6 and 7, the specification only teaches such a construct wherein the nucleotides -183 to +25 are missing from SEQ ID NO:1. The recitation in claim 6 of -183 and +25 more particularly are only relevant when describing SEQ ID NO:1. As to reporter genes, there are numerous reporter genes that are known in the art. However, only one of these provides a detectable product by addition of the substrate to the medium of cultured cells and this is beta-lactamase. Typically, reporter genes are assayed by harvesting the cells, producing a lysate and detecting the enzymatic activity. Hence, applicants lack written description of a genus of such reporter genes.

Both the reporter gene and the transcription regulatory sequences recited in the claims are species of nucleic acid sequences that cannot be envisioned any better when the possible choices are narrowed from all possible sequences to all possible sequences with a known functional property. Hence, while it is known that the reporter gene must convert a substrate to detectable product and the transcriptional regulatory sequences must be responsive to HDAC inhibitors Apicidin, Trichostatin A, sodium butyrate, SAHA and MS27-275, claiming all DNA's that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. In this case, applicants claim a genus of promoter that is not structurally described in the specification such that the nexus between structure and function are known. And an adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., Univ. of Rochester v. G.D. Searle & Co., 358 F.3d

916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described."). In other words, it is not sufficient to define an agent solely by its principal biological. Therefore, there is no disclosure of a structure-function relationship between the sequence of SEQ ID NO 1 and any transcriptional regulatory sequence as recited. Given the large size and diversity of the sequences as well as reporter genes recites and the inability to determine which will also have the essential element, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of one species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 5 is rejected under 35 U.S.C. 112, first paragraph, because the specification in claim 8 refers to biological deposits to satisfy the "how to make" requirement, but fails

to specify the details of the cell line such that one of skill in the art can produce the recited cells.

More particularly, claim 5 is drawn to or encompasses use of cells that are ICLC PD02008 which are recombinant HeLa cells containing the reporter gene .beta.-lactamase operably linked to a p21 minimal promoter which comprises the nucleotide sequence set forth in SEQ ID NO:1. As such, this application discloses a cell lines that is encompassed by the definitions for biological material set forth in37 C.F.R. 1.801. Because it is apparent that this biological material is essential for practicing the claimed invention, it must be obtainable by a reproducible method set forth in the specification or otherwise be known and readily available to the public as detailed in 37 C.F.R. 1.801 through 1.809.

It is unclear that the cells of claim 5 will be readily available to the public or that the written instructions are sufficient to reproducibly construct this biological material from starting materials known and readily available to the public. Therefore, in order for a deposit to meet all criteria set forth in 37 C.F.R. 1.801 through 1.809, Applicant or Assignee must provide assurance of compliance with provisions of 37 C.F.R. 1.801-1.809 in the form of a declaration or Applicant's representative must provide a statement. The specification states that the cells are "deposited at the Centro di Biotecnologie Avanzate (CBA), Interlab Cell Line Collection (ICLC), Servizio Biotecnologie, L.go Rosanna Benzi, 10, 16132 Genova, Italia on Nov. 20, 2002, under the terms of the Budapest Treaty as deposit ICLC PD02008." However, it is unclear that applicants themselves have deposited the cells and should this be the case, the specification does not indicate that the cells will be and that the cells will be irrevocably and without restriction or

condition released to the public upon issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR1.808. Further, the record must be clear that the deposit will be maintained in a public depository fro a period of 30 years after the date of the deposit, 5 years after the last request for a sample or for the enforceable life of the patents whichever is longer. See 37 CFR 1.806. Because such deposit will not have been made prior to the effective filing date of the instant application, Applicant is required to submit a verified statement from a person in a position to corroborate the statement that the biological material which had been deposited is the biological material specifically identified in the applicants as filed (37 C.F.R. 1.804). Such a statement need not be verified if the person is an agent or attorney registered to practice before the Office.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
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> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2 and 10 are rejected under 35 U.S.C. 102(e) as being anticipated by Jarecki et al (20050065173; see entire document).

Jarecki et al teach use of a mammalian cellular assay (see e.g. ¶ 150) with a stably integrated SMN2-beta-lactamase construct. BLA activity was stimulated by addition of

sodium butyrate (see e.g. ¶ 190). Additional compounds were assayed using this system (see e.g. last line, ¶ 190). Beta-lactamase operates inherently by acting on a substrate wherein a detectable product in the cell is observed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6-8 and 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jarecki et al (20050065173; see entire document) in view of any of Tang et al (JBC, 1998, Vol 273(4), pages 29156-29163; see entire document), Emerson et al (US 20030228627; see entire document) and Pallaoro et al (US 20080057529; see entire document).

The instant invention is drawn to a method of identifying an analyte that is a histone deactylase inhibitor (HDAC). The method requires use of a cell that is stably transfected with a promoter wherein the cell is cultured with substrate for the reporter and an analyte.

While Jarecki et al teach use of a promoter-reporter construct that is stably integrated into a cell, it does not teach all of the limitations of all of the claims. However, the art demonstrates that basic method of the invention is known in the art and the limitations are but variations on components of the method. Specifically, the instant

claims recite that the promoter that is responsive to HDAC inhibitors Apicidin, Trichostatin A, sodium butyrate, SAHA and MS27-275 is p21 and preferably one lacking the p53 responsive elements. Secondly, the claims recite that the cell used in the cell based assay can be Hela or MCF7 and finally that the lactamase reporter acts on a substrate with a cephalosporin cleavage site and is labeled with a donor:activator fluorophore pair capable of fluorescence energy transfer.

Tang et al teach a p21 promoter- reporter construct that lacks the p53 responsive elements that is introduced into MCF7 cells (see e.g. bridging ¶ 29156-29157 and page 29157, col 2, last ¶). The cells were treated with analyte and reporter gene expression measured (see e.g. figure 3). Such a promoter element encompasses claim 7 which recites that the regulatory includes (open) the -183 to +25 sequences of p21. As well, the p21 promoter is from human and absent evidence to the contrary one would expect the sequence to comprise SEQ ID NO:1.

Emerson et al teach use of a human-p21-reporter construct, which is inherently responsive to Apidicin, Trichostatin A, sodium butyrate, SAHA and MS27-275. in mammalian cells such as human cells for detection of reporter gene activity (see e.g. ¶ 0053 and 0062). Reporter genes include beta-lactamase (see e.g. ¶30). The sequence of the p21 reporter is human p21 and hence would absent evidence to the contrary comprise SEQ ID NO:1.

Pallaoro et al teach that lactamase acts on a substrate comprising a cephalosporin cleavage site labeled with a donor:acceptor pair of fluorophores capable of FRET in the intact substrate which are situated on opposite sides of the cleavage site and detection of

fluorescence produced by the donor fluorophore when the substrate is cleaved (see e.g. ¶ 0064).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include the substrate for lactamase as taught by Pallaoro in the assay of Jarecki et al or to modify the system of Emerson and Tang et al with the teachings of Jarecki et al such that the promoter-reporter is stably integrated into the cell as taught by Jarecki et al because the art teaches that use of promoter-reporter constructs in cell based assays (such as in MCF7) was well known in the art and because the art teaches that a p21 promoter lacking p53 binding sequences as well as lactamase reporter constructs comprising cephalosporin cleavage site labeled with a donor:acceptor pair of fluorophores capable of FRET were also well known. The combination of the references thus demonstrates an attempt to use known techniques to improve similar methods using skills that were available at the time of filing with well-established methods on well-characterized sequences and cells. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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